

AD-A234 902



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MIPR NO: 90MM0522

TITLE: A PILOT STUDY: EVALUATION OF THE EFFECTS OF TREATMENT
WITH 0.75% TOPICAL CAPSAICIN IN PATIENTS WITH REFLEX
SYMPATHETIC DYSTROPHY USING THREE PHASE BONE
SCINTIGRAPHY

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REPORT DATE: January 28, 1991

TYPE OF REPORT: Final Report

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ELECTE
APR 15 1991
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PREPARED FOR: U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;
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91 4 15 042

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION Unclassified			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY			3. DISTRIBUTION / AVAILABILITY OF REPORT Approved for public release; distribution unlimited		
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE					
4. PERFORMING ORGANIZATION REPORT NUMBER(S)			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
6a. NAME OF PERFORMING ORGANIZATION Brooke Army Medical Center		6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION		
6c. ADDRESS (City, State, and ZIP Code) Nuclear Medicine Service Fort Sam Houston, TX 78234-6200			7b. ADDRESS (City, State, and ZIP Code)		
8a. NAME OF FUNDING / SPONSORING ORGANIZATION U.S. Army Medical Research & Development Command		8b. OFFICE SYMBOL (If applicable) SGRD-RMI-S	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER MIPR No. 90MMO522		
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, Maryland 21702-5012			10. SOURCE OF FUNDING NUMBERS		
			PROGRAM ELEMENT NO. 61102A	PROJECT NO. 3M1- 61102BS12	TASK NO. AZ
			WORK UNIT ACCESSION NO. WUDA331029		
11. TITLE (Include Security Classification) A Pilot Study: Evaluation of the Effects of Treatment with 0.75% Topical Capsaicin in Patients with Reflex Sympathetic Dystrophy Using Three Phase Bone Scintigraphy					
12. PERSONAL AUTHOR(S) Stuart E. Sinoff, M.D., MAJ; and Mary B. Hart, M.D., MAJ					
13a. TYPE OF REPORT Final Report		13b. TIME COVERED FROM 1/15/90 to 9/30/90		14. DATE OF REPORT (Year, Month, Day) 1991 January 28	
15. PAGE COUNT #8					
16. SUPPLEMENTARY NOTATION					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP			
06	05		Capsaicin; Causalgia; Reflex sympathetic dystrophy; Dysesthetic pain, RA III		
19. ABSTRACT (Continue on reverse if necessary and identify by block number)					
<p>Eight patients with dysesthetic pain were treated in an open trial with capsaicin 0.075%, including five patients with reflex sympathetic dystrophy, and one each with meralgia paresthetica, thalamic pain syndrome, and multiple sclerosis. Pain relief and functional impairment were assessed by visual analogue and functional capacity scales respectively. At the end of the study period, pain relief in the RSD group averaged 73%; impairment score declined by 60%. Abnormalities of pretreatment bone scintigraphy reversed in patients with symptoms of less than eight months duration. In patients with RSD and other</p>					
20. DISTRIBUTION / AVAILABILITY OF ABSTRACT <input type="checkbox"/> UNCLASSIFIED/UNLIMITED <input type="checkbox"/> SAME AS RPT <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified		
22a. NAME OF RESPONSIBLE INDIVIDUAL Mrs. Virginia Miller			22b. TELEPHONE (Include Area Code) 301/663-7325		22c. OFFICE SYMBOL SGRD-RMI-S

19. Abstract (Continued)

dysesthetic pain syndrome topical capsaicin may specifically relieve superficial, burning, dysesthetic pain, a major factor in the physical and emotional disability seen in this syndrome. The spectrum of capsaicin's current clinical use is discussed.

On the basis of the results of this study we recommend larger, controlled and blinded studies to assess further the efficacy of topical capsaicin in dysesthetic pain syndromes. ✓

Accession For	
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Unannounced	<input type="checkbox"/>
Justification	
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Distribution/	
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Principal Investigator's Signature Date 1/28/91

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CAPSAICIN AND DYSESTHETIC PAIN

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Key Words: capsaicin, causalgia, reflex sympathetic dystrophy, dysesthetic pain.

This work was supported by the U.S. Army Medical Research and Development Command.

The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

In the conduct of research where humans are the subjects, the investigators adhered to the policies regarding the protection of human subjects as prescribed by 45 CFR 46 (Protection of Human Subjects).

Financial Disclosure/Proprietary Statement: Capsaicin 0.075% is manufactured by the GalenPharma, 2905 MacArthur Blvd., Northbrook, IL 60062. Our points of contact at GalenPharma have been the director of medical research, John Kallal PhD. They arranged for the donation of capsaicin 0.075% by GalenPharma in the present study. They did not otherwise donate funds or other resources to the investigators, the U.S. Army, or other parties in association with this pilot study. We do not hold common stock in, or have other financial interest in GalenPharma or the product **Axsain** (capsaicin 0.075%).

NOTE: The sections to follow are set up in a format similar to that required by scientific journals. The information herein encompasses both the clinical findings in patients in the open trial, as well as the radiographic findings which will be prepared in separate manuscripts for publication. The discussions are somewhat longer, of greater detail, than the more discrete versions that will be submitted for publication.

ABSTRACT: 8 patients with dysesthetic pain were treated in an open trial with capsaicin 0.075%, including 5 patients with reflex sympathetic dystrophy (RSD), and 1 each with meralgia paresthetica, thalamic pain syndrome, and multiple sclerosis. Pain relief and functional impairment were assessed by visual analogue and functional capacity scales respectively. At the end of the study period, pain relief in the RSD group averaged 73%; impairment score declined by 60%. Abnormalities of pre-treatment bone scintigraphy reversed in patients with symptoms of less than 8 months duration. In patients with RSD and other dysesthetic pain syndromes, topical capsaicin may specifically relieve superficial, burning, dysesthetic pain, a major factor in the physical and emotional disability seen in this syndrome. The spectrum of capsaicin's current clinical use is discussed.

INTRODUCTION

The term causalgia was first proposed by Dunglison¹, originally described by Mitchell, Morehouse and Keen in 1864² and further elucidated by S. Wier Mitchell in 1872.³ It consists of burning pain in a hyperesthetic, swollen extremity, the skin of which has a "glossy redness". With time, progressive atrophy of skin, muscle and bone, and nail dystrophy occur. Reflex Sympathetic Dystrophy (RSD), while encompassing the causalgias, is a categorization that (incorrectly) presumes a known pathophysiology, simultaneously referring to sympathetic hyperactivity as well as a favorable response to sympathetic blockade, consistent features of these disorders. The clinical syndromes of RSD, which encompasses a heterogeneous group of disorders with a wide spectrum of symptoms and severity, are thoroughly reviewed elsewhere.²⁻⁶

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is reported to be effective in the treatment of various dysesthetic pain syndromes, including postherpetic neuralgia, post-mastectomy pain, and diabetic neuropathy.⁷⁻¹¹ The similarity of pain in RSD to pain syndromes which have responded favorably to topical capsaicin led to a therapeutic trial in a patient with RSD and, subsequently, to an open trial in patients with RSD and non-RSD (NRSD) dysesthetic pain.

Subjects and Methods:

Patients treated with topical capsaicin fell into one of two groups: 1) RSD - by history, physical examination, and acute relief with sympathetic blockade or 2) NRSD - by history and examination, pain having a superficial burning and hyperesthetic quality.

Three women and two men with RSD, ages 32,34,40,68 and 70 years, applied capsaicin cream topically four times per day to the affected area. Pain had been present from 10-216 months (average 5.5 years). A sixth patient discontinued treatment due to side effects of capsaicin.

There were three patients in the NRSD group. M.N. described 10 years of constant bilateral burning over the anterolateral thighs due to meralgia paresthetica. H.W. gave a history of 13 years of right upper and lower extremity burning pain after a thalamic infarction. J.T. presented with four months of superficial, burning pain over an hyperesthetic right breast, chest, and upper abdomen which was likened to the "burning of fire ants" (bites). Clinical and paraclinical evidence of multiple CNS lesions were present. MRI revealed multiple areas of increased signal in the cerebral white matter and in the central portion of the spinal cord at the level of C2. Over the counter analgesics and tricyclics had no appreciable affect on her pain.

Pretreatment evaluations for both groups included a history and neurologic examination by a neurologist (S.E.S.). All 8

patients treated with topical capsaicin met the criterion of experiencing superficial, burning dysesthetic pain. Pretreatment medications and treatments were noted, and in the RSD group, response to sympathetic ganglion blockade was determined. All patients in the RSD group underwent pretreatment three phase bone scintigraphy (TBPS). Pretreatment pain was rated by visual analogue scale (VAS), an established method of evaluating pain and pain relief, previously used in the evaluation of RSD.¹²⁻¹⁴ Patients were asked to mark along a 10 cm horizontal line labelled at the far left "no pain", and at the far right "maximum possible pain" (see figure 1.). Functional impairment was rated by functional capacity scales (FCS). Amount of interference with eating, sleeping, walking, shoe and sock use, work related to job or household chores, and recreational activities were rated as none (0), slight (1), moderate (2) or severe (3). Maximum FCS score for all six categories was 18, minimum 0. Table 1 summarizes patient profiles in both groups.

Capsaicin 0.075% was applied topically to the skin over the area(s) of superficial, burning dysesthetic pain four times per day. Treatment in the RSD group ranged from 10 to 24 weeks (average - 20 weeks). Other medications were unchanged during the treatment period, and dosages of current medications were maintained at pre-treatment levels in all patients. Non-pharmaceutical pain therapies such as transcutaneous nerve stimulation, contrast baths and other "counter-irritant" treatments were not permitted during the treatment period.

Post-treatment evaluation included follow-up physician evaluations (M.B.H & S.E.S.) at 2,6,10,14,18, and 24 weeks after entry and included ratings of pain by VAS and functional impairment by FCS. In addition, pain relief was rated by VAS; patients were asked to mark a 10 centimeter vertical line labelled "no relief" and "complete relief" at the bottom. Subjects were asked specifically to rate the *superficial, burning dysesthetic* pain. They were asked about the existence of other qualities of pain. Any changes in medications were noted. TBPS was obtained for each of the RSD subjects at the termination of treatment, approximately 24 weeks.

Results:

RSD. Table 2. lists the pain ratings at entry, 2 weeks and subsequent four week intervals. Average pain experienced (percent of max possible by VAS) for RSD patients at entry was 62.5%. This declined to 48.5% at 6 weeks, and 27.1% at the termination of treatment. Average pain relief in the RSD group at 6 weeks was 62.3%, and 73.3% at the end of the study (table 3). Functional capacity scores averaged 10.6 at entry in the RSD group, 5.6 at 6 weeks, and 4.2 at termination. This represents a 61% improvement over entry (table 4). In addition to dysesthetic pain, most patients reported transient or chronic pain that was deep aching, shooting, or lancinating which was *not modified by topical capsaicin*.

W.H., who demonstrated a significant clinical response at week 6, suffered a new injury to his left upper extremity in April of 1989 (week 9 of capsaicin treatment). After falling on his left shoulder and arm he had markedly decreased strength in the hand, and an exacerbation of shoulder and arm pain. Wasting of intrinsic muscles in the left hand became prominent. EMG showed chronic changes in all myotomes served by the brachial plexus and acute denervation in C8 and T1 innervated muscles. He continues to benefit from capsaicin applied to the hand and arm, but has never again regained function. W.H.'s scores are included in the overall results. If his scores had been calculated from week 6, prior to the reinjury, the average functional disability score in the RSD group would have been 3.0

(72% improvement over entry vs 61%).

Non-RSD Dysesthetic Pain. Total average scores for pain experienced, pain relief and functional disability were similar to the RSD group (tables 2-4). M.N. (bilateral meralgia) achieved 95% relief of pain by week 6 and 100% relief at termination. J.T. (multiple sclerosis) stopped capsaicin on two occasions; the pain returned to baseline intensity within 6 days each time. Within a week of restarting treatment her pain lessened. At ten weeks of treatment she rated pain relief (VAS) to be 82%. H.W. (thalamic pain) rated pain relief at approximately 18%; his functional disability did not change appreciably over 6 months of treatment.

Side Effects. All patients reported a superficial burning, of variable severity, with application of capsaicin. This diminished rapidly over the first several days of treatment and was most pronounced with contact of mucous membranes and intertriginous areas. Perspiration increased this discomfort which is also described as superficial and burning, but easily separable from baseline dysesthetic pain.

When applied to normal, unbroken skin, it produces a mild to moderate sensation of warmth and burning which develops after 5-15 minutes, and which may last hours. Data from healthy controls show that all subjects experience burning pain from capsaicin during the initial phase of treatment, usually lasting 30-60 minutes.¹⁵

One of the RSD patients dropped out in the first days of

treatment because of unacceptable burning sensations. Although not specifically measured, it was our impression that patients with the most intense burning in response to capsaicin achieved the most remarkable responses.

One patient had a maculopapular eruption at four weeks of treatment. The cream was stopped for several days, but on rechallenge, the rash did not develop and the patient wished to continue treatment.

Bone Scanning. In patients C.Y. and L.B. baseline studies show the classical findings of RSD: increased arterial flow, increased blood pool, and on delayed imaging, prominent periarticular uptake in the affected region. After 20 weeks of topical capsaicin these two studies normalized, except for a focal area of increased blood pool and bone labelling in L.B.'s right great toe. Of interest is her clinical course. At entry L.B. had burning, dysesthetic pain in the right foot. She applied capsaicin four times daily to the instep and ankle, the areas of greatest discomfort, but not to the great toe, which was affected to a lesser degree. At termination, her pain had resolved entirely except for mild residual burning over the great toe. Notably, patients C.Y. and L.B. had the shortest duration of symptoms: 4 months and 8 months respectively.

W.H., the patient with the longest duration of symptoms (18 years), and who suffered a reinjury to the affected limb, had a baseline bone scan with mild decreased blood flow and blood pool as well as decreased uptake on the 3 hour delayed images. These

findings did not change significantly with treatment.

In the remaining two RSD patients, in whom symptoms had been present for 2.2 and 12 years respectively, symmetric activity in affected and contralateral extremities was noted on the pretreatment as well as follow-up TPBS studies.

Discussion:

In recent years topical capsaicin has recieved growing attention in the treatment of specific pain syndromes. Derived primarily from neonatal and adult rat models, there is a growing fund of information regarding capsaicin's ability to deplete substance P and to alter the function (and perhaps the structure) of the sensory neuron and its peripheral and central processes. The best documented of capsaicin's physiologic effects is its ability to deplete the neuropeptide substance P in small sensory neurons and their termini in the CNS.¹⁶⁻²³ This has been shown in skin¹⁸, saphenous and vagus nerves¹⁹, dorsal roots^{19,22}, cornea¹⁹, and coeliac ganglion²³. Similar, and generally parallel, depletions have been shown for cholecystokinin.¹⁶⁻²³ A review this area is beyond the scope of this report, but the insights gained regarding capsaicin's physiologic effects have, at best, a tenuous relationship to possible mechanisms of an individual's experience of pain. We are far from understanding the dynamic interplay between the reception of sensory information and the multi-level processing that leads to a central representation of pain.

Effects of capsaicin on human subjects. Capsaicin applied to the skin of human subjects brought about a decrease in heat threshold of 3.5⁰C within 10 hours.²⁴ 2-10 days later a 2⁰ increase in heat threshold was demonstrated. In a recently completed series of experiments at Oregon Health Sciences

University, Simone and Ochoa evaluated the effects of capsaicin (0.075%) applied to a 4 cm² patch of skin on the forearms of normal human volunteers against vehicle-controls.¹⁵ Parameters included threshold for pain induced by mechanical pressure, pain sensation induced by mechanical pricking, thermal specific and thermal pain sensations (warmth, cold, heat pain and cold pain), suprathreshold heat pain and histamine-induced itch and flare. Neither tactile detection thresholds nor pain induced by pricking or by pinching were modified by capsaicin or vehicle. Thresholds for detection of warmth sensation became significantly elevated in capsaicin treated skin beginning on the day following the first treatment, and continued to increase during the first four weeks of application. Both heat pain thresholds and the magnitude of suprathreshold heat pain were altered significantly in skin treated with capsaicin. Detection thresholds for sensations of cold and cold pain were not changed significantly. Also unchanged by the application of capsaicin were the sensation of itch or the area of flare produced by injection of intradermal histamine. After discontinuing capsaicin, warmth thresholds returned to baseline values within two weeks. Heat pain sensation became significantly diminished in capsaicin treated skin.

Capsaicin treatment for pain:

Postherpetic Neuralgia. Watson et al conducted an uncontrolled trial of topical capsaicin in 33 patients with postherpetic neuralgia.⁷ Approximately one-third terminated the

study prematurely because of burning associated with topical application of capsaicin. Of 23 patients completing the trial, 78% noted some improvement, 56% having "good or excellent" pain relief after 4 weeks. In a 6 week controlled trial in 32 patients with postherpetic neuralgia, Bernstein et al demonstrated a 77% response rate with topically applied capsaicin (0.025%) vs the vehicle-treated (placebo) response rate of 31%.⁹ By 6 weeks 46% of patients reported pain relief as measured by VAS compared to 6% in the vehicle-treated group. Successful use of topical capsaicin in intraoral postherpetic neuralgia has also been described.²⁵

Postmastectomy pain syndrome (PMPS): After 4 weeks of topical capsaicin (0.025%) 12 of 14 women with PMPS reported some level of relief, judged to be "good or excellent" in 57%.¹⁰

Diabetic Neuropathy: An 8 week multicenter double-blinded and placebo-controlled study of topically applied capsaicin in 252 patients with painful diabetic neuropathy was recently completed.¹¹ Capsaicin (0.075%) was significantly better than vehicle-control in overall clinical improvement assessed by a physician, pain severity, and pain relief. Other trials in diabetic neuropathy are underway.

Headache: In an interesting trial in Florence, episodic and chronic cluster headache patients reportedly achieved some relief after intranasally administered, dilute capsaicin.²⁶ Normal controls demonstrated similar side effects and time course of desensitization to the discomfort of intranasally administered

capsaicin, but the absence of untreated cluster headache controls makes the evaluation of treatment difficult in a naturally remitting illness. In 5 of 7 chronic cluster patients, having continual symptoms for the 6 months prior to treatment, the remission of symptoms for 28-40 days and subsequent return of previous pain is very interesting, but again, suitable untreated chronic cluster controls were not used.

Relation among dysesthetic pain syndromes: In 1984 Asbury and Fields proposed the division of neuropathic pain into two distinct categories: dysesthetic and nerve trunk.²⁷ In their formulation, nerve trunk pain results from activity in normal nociceptive endings within the nerve trunks (nervi nervorum). Pain is described as an "aching", or "tender", "familiar" pain, like a toothache, which feels better when an optimal position is achieved. Dysesthetic pain is a "burning, tingling, raw, electric and "unfamiliar" experience. (table 5) Their examples of dysesthetic pain, in 1984, included causalgia, small fiber neuropathy and postherpetic neuralgia, unwittingly predicting the response of dysesthetic pain syndromes to capsaicin. The first published response of postherpetic neuralgia to capsaicin was in 1987, of postmastectomy pain in 1989, of small fiber neuropathy in 1990 (submitted for publication), and in causalgia, the present report.

Counter-irritant treatments in causalgia: The burning experienced with application of capsaicin suggests the possible role of counter-irritation in its pain modulating activity.

Standard treatment of causalgic pain (RSD) focuses on mobilization of the involved extremity utilizing passive range of motion, physical and occupational therapy, and counter-irritation, by such means as contrast baths and transcutaneous nerve stimulation. Therapy of causalgia has its roots in S. Wier Mitchell's civil war experience beginning at the United States Army Hospital for Diseases on Christian Street, Philadelphia in 1863.³ In the treatment of traumatic nerve injuries from missile wounds, nerve compressions received decompressive surgery and those with "an inflammatory state of the nerve" were treated with "rest, enforced by a splint". "Morphia" was recognized by Mitchell to be the sole effective narcotic. Electric current was an accepted treatment, both "induced" and the preferred "rapidly reversed galvanic current". In addition to narcotic injections, neurotomy, and limb amputation, effective treatments for causalgia were counter-irritant in nature: water-dressings, hot turpentine rags, shampooing ("rubbing"), blistering, continuously applied cold packs, and counter-irritant lotions. Mitchell remarks, "I do not know why we gain by using an irritant over very large surfaces, extending far beyond the region involved; but advantage certainly seems to arise from it."³ Blistering with Granville's lotion or cantharides ("spanish fly" or "russian flies") was the single most effective treatment.

Bone Scanning and RSD. One of the difficulties in assessing response to therapeutic intervention in chronic pain is the paucity of objective and quantifiable measures. There is a rich

literature regarding TPBS and RSD from which to take guidance.²⁸⁻

^{36.} Demangeat et al suggest a classification of three scintigraphic stages of RSD based on TBPS from 181 patients with that disorder.³⁵ In stage I, 0-20 weeks from onset of symptoms, there is increased activity in the affected limb, in arterial flow, blood pool, and delayed images. Stage II, from 20-60 weeks, is characterized by normalization of arterial flow and blood pool activity, but increased periarticular labelling persists in delayed images. During stage III, from 60-100 weeks, flow and blood pool activity tend to become reduced on the affected side and the pattern of juxtaarticular uptake may become symmetric or decreased on the affected side. Initially we hypothesized that TPBS would provide an objective measure of response to therapy. Bone scans in some patients did not suggest a specific diagnosis of RSD, apparently related to the long duration of symptoms. Importantly, our data support Demangeat's staging of RSD. In patients C.Y. and L.B., who had symptom durations of 4 and 8 months respectively (Demangeat stage I), TBPS was most helpful. The reversal of pretreatment abnormalities correlated clinically. The remainder of RSD patients completing the study had an average pretreatment symptom duration of 106 months, and would be expected by Demangeat's observations to have normalized or reversed bone scan abnormalities classically associated with RSDs. Although the experience is limited, our results support the possibility that TBPS would be a useful indicator of response in those patients with symptoms for less than 32 weeks duration,

and perhaps up to 60 weeks.

In summary, the results of a 6 month open trial of topically applied capsaicin (0.075%) in RSD and NRSD dysesthetic pain show marked lessening of pain and significant functional improvement. Effects were delayed, most often occurring between 2 and 4 weeks after treatment. Notably, *topical capsaicin did not relieve non-dysesthetic pain in these patients.* Results in the NRSD group were mixed. The patient with thalamic pain did not appear to derive benefit. The one other patient with a presumed central cause of dysesthetic pain, secondary to multiple sclerosis, described considerable improvement, as did the patient with meralgia paresthetica.

Response to topical capsaicin of postherpetic neuralgia, postmastectomy pain, painful polyneuropathy, RSD, and NRSD dysesthetic pain, all of which have superficial, burning, "unfamiliar" qualities, supports an hypothesis of Asbury and Fields that these represent a distinct type of pain, sharing a common pathophysiology.

Topically applied capsaicin requires physical manipulation of the skin and causes discomfort with administration. Before attributing a unique physiologic mechanism to capsaicin's action in pain syndromes, such as the depletion of neuropeptides, capsaicin must be compared in controlled trials to other counter-irritants.

The clinical course of RSD is variable, but we believe that

the results of the present pilot study are suggestive of efficacy and should be followed by large, blinded and controlled trials.

TPBS may be most helpful in the early stages of RSD, when vascular physiology is acutely altered. Abnormalities may be more readily reversed prior to the onset of severe dystrophic changes, and scintigraphy may provide an objective measure of response to therapy in further clinical trials.

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Organization of Figures, Tables and Legends:

Figure 1.

No pain ————— Maximum pain

Legend for figure 1.

"visual analogue scale"

TABLE 1

CLINICAL DATA

<u>pat</u>	<u>age/ sex</u>	<u>symptom duration</u>	<u>affected area/precipitant</u>	<u>SGB*</u>
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REFLEX SYMPATHETIC DYSTROPHY

L.B.	70/F	10 mo	R foot & ankle/trauma from fall	+
C.Y.	34/M	4.5 mo	R arm & hand/after carpal tunnel release	+
S.W.	39/F	24 mo	R ankle/after cellulitis	+
W.H.	68/M	216 mo	L upper extremity, esp ulnar aspect from shoulder to hand/after 1 st rib resection	+
B.C.	32/F	78 mo	L upper extremity, ulnar aspect forearm/ after L ulnar nerve transposition	+

OTHER DYSESTHETIC PAIN SYNDROMES

M.N.	46/M	120 mo	proximal anterolateral thighs/ bilateral myralgia paresthetica	N/A
H.W.	64/M	156 mo	right upper and lower extremity thalamic pain syndrome	N/A
J.T.	50/F	4 mo	right breast & chest/M.S.- C2 cord lesion	N/A

*SGB = relief with stellate ganglion blockade

TABLE 2

% PAIN EXPERIENCED (% OF MAX): VISUAL ANALOGUE SCALES

PATIENT	SCR	WK2	WK6	WK10	WK14	WK18	WK24
<u>REFLEX SYMPATHETIC DYSTROPHY</u>							
L.B.	47	16	57	22.5	19	8	
C.Y.	72	38.5	73.5	76.5	68.5	8	5.5
S.W.	99.5	78	57	76.5	50	70	51
W.H.	76	56	51	61.5	67.5	63	64
B.C.	18	14	4	7			
<u>OTHER DYSESTHETIC PAIN SYNDROMES</u>							
M.N.	25	40	13	7.5	10	7.5	0.0
H.W.	84.5	54	82	77	83		90
J.T.	67	31.5	22.5				

TABLE 3

PAIN RELIEF (%) BY VISUAL ANALOGUE SCALES

PATIENT	WK2	WK6	WK10	WK14	WK18	WK24
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REFLEX SYMPATHETIC DYSTROPHY

L.B.	82	76	82	93	93	
C.Y.	39.5	32	70.5	43.5	88	96
S.W.	25	51	48	55.5	29.5	50
W.H.	25.5	58.5	63	63	90	36
B.C.	27.5	94	91.5			

OTHER DYSESTHETIC PAIN SYNDROMES

M.N.	63	95	99.5	94	91.5	100
H.W.	83	15	26	14	21	13
J.T.	77	78	82			

TABLE 4

FUNCTIONAL DISABILITY: FUNCTIONAL CAPACITY SCALES*max score = 18*

PATIENT	SCR	WK2	WK6	WK10	WK14	WK18	WK24
<u>REFLEX SYMPATHETIC DYSTROPHY</u>							
L.B.	14	10	7	7	2	0	
C.Y.	6	2	5	5	4	3	0
S.W.	11	12	8	8	9	12	7
W.H.	15	9	8	12	18	15	14
B.C.	7	0	0	0			
<u>OTHER DYSESTHETIC PAIN SYNDROMES</u>							
M.N.	4	5	3	1	2	3	2
H.W.	12	9	7	13	16	14	10
J.T.	2	1	4	1			

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